Inter-firm R&D partnering in high technology industries - patterns in the international biotechnology industry since 1975

4. Inter-firm R&D partnering in high technology industries

Nadine Roijakkers and John Hagedoorn

Until recently, R&D was not an activity that researchers expected to see carried out in cooperation between different companies. In particular for high technology industries, such as IT and biotechnology, where state-of-the-art research and technological know-how are critical to competitive success, the sharing of R&D activities by competing companies seemed a rather unusual aspect of corporate behaviour. This is probably one of the main reasons why the growth of the number of inter-firm R&D partnerships during the 1980s and the 1990s has attracted so much attention in recent years, both in the academic literature and in the popular press.

We will attempt to contribute to the understanding of inter-firm collaboration in R&D with an analysis of some basic trends and patterns in the forming of R&D alliances in the international biotechnology industry. The biotechnology industry is one of the main examples of current industries where we find a large number of R&D alliances, in particular between large and small companies (Hagedoorn, 1996a; Hagedoorn and Roijakkers, 2002; Kenney, 1986; Powell, 1996). Data from the MERIT-Cooperative Agreements and Technology Indicators (CATI) database (see Appendix 4.1) suggest that over 65 per cent of all the biotechnology R&D alliances are related to pharmaceutical biotechnology. Because of the dominance of this particular sub-sector in the biotechnology industry, with so few alliances found in other biotechnology sectors, our contribution focuses on collaboration between companies in the pharmaceutical biotechnology industry.

Apart from a sectoral restriction we will also limit the analysis to those inter-firm agreements for which the transfer of technology or the creation of new technology through R&D are central to the agreement. R&D refers to the standard research and development activities that are aimed at increasing scientific or technical knowledge and the application of that knowledge to the creation of new and improved products and processes. We will confine the analysis to particular modes of partnering such as joint ventures for which common R&D or technology sharing is a major objective, joint R&D agreements, and minority holdings coupled with research

contracts. We have chosen the period from 1975 to 1998 because this covers the years in which inter-firm partnering has risen rapidly, in biotechnology as well as in many other fields of technology and sectors of industry (Hagedoorn, 1996a).

Throughout this chapter we will refer to the biotechnology 'industry' although this is probably an incorrect term as its status as a separate industrial sector is still somewhat unclear. Strictly speaking, biotechnology is not yet a full industrial sector but a hybrid form of an 'industry' with established companies, such as from the pharmaceutical sector, and a wide range of new biotechnology companies that are science based and technology driven but still with relatively few regular products and limited manufacturing capabilities (Powell, Koput and Smith-Doerr, 1996). In other words, when we use the term industry in the following analysis, we recognize that we are mainly analysing the behaviour of a group of companies that are engaged in R&D, innovation and the manufacturing of products and processes that can be labelled as biotechnological activities.

In the following we first present and explain the growth pattern in R&D partnering since 1975. This is followed by a discussion of the major factors that could motivate companies to enter into various sorts of R&D partnerships. Although the rationales for cooperation are numerous we restrict our attention to those rationales that are important for firms in the biotechnology industry (see Hagedoorn, 1993 for a more general overview of motives for R&D partnerships). The next section is devoted to a discussion of the different organizational features of basic categories of modes of cooperation. In that section we also pay attention to the analysis of changes in the distribution of different categories of partnerships. Next, we discuss international patterns of partnering in terms of changes in the historical distribution of domestic and international partnerships, with special reference to the Triad regions (Asia, Europe, and North America). Finally, we pay some attention to the role played by large and small companies in the context of the most R&D cooperation-intensive companies in the biotechnology industry. The closing section presents some conclusions.

HISTORICAL PATTERN OF R&D PARTNERSHIPS

In order to assess the importance and magnitude of alliance activity we examine the number of newly established R&D partnerships as they appear in the CATI database. Figure 4.1 shows the growth pattern of annually newly made R&D partnerships in the biotechnology industry for the period 1975–98. The numbers are calculated as three-year moving averages to show the general trend in the data while correcting for yearly fluctuations.

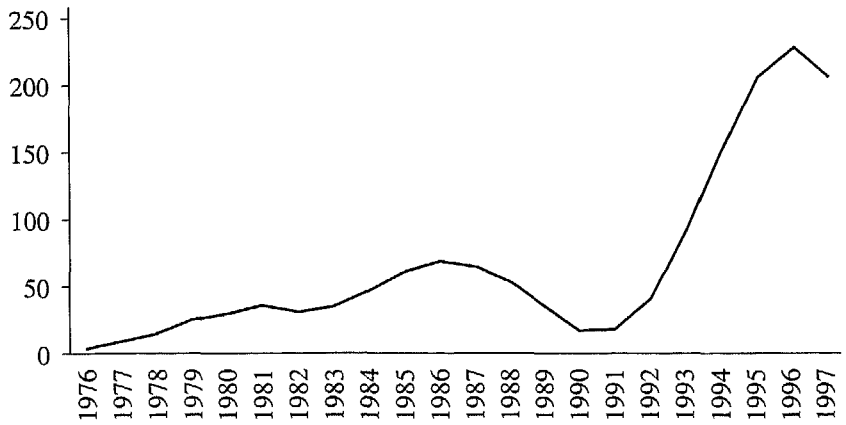

Figure 4.1 Growth of newly established R&D partnerships, three-year moving averages, 1975–98

During the second half of the 1970s, there was a gradual increase in the number of newly established R&D partnerships from fewer than five in 1976 to around 15 new agreements in 1978. The end of the 1970s witnessed a rather sudden increase in the number of new partnerships as nearly 25 alliances were established in 1979. This particular growth pattern continued well into the first half of the 1980s. Apart from a small drop in 1982, those years marked a rather steep increase in the number of annually formed partnerships from about 30 in 1980 to nearly 70 new alliances made in 1986. The last couple of years of the 1980s showed a substantial drop in the newly made R&D partnerships to slightly more than 35 in 1989. During the early 1990s the number of newly made alliances dropped even further to fewer than 20 in 1991, after which the number took off again to reach a level of about 230 new partnerships in 1996. At the end of the period of our analysis, the number of annually made alliances was decreasing again to just over 200 new partnerships in 1997. However, this number is still considerably higher than the figures found for most years since the early 1980s.

All in all, the historical data on R&D partnering in the biotechnology industry revealed, despite some irregularities, an overall growth pattern in the number of annually made R&D partnerships since the mid-1970s. During the late 1970s there was a rather steady growth pattern, while the 1980s and particularly the 1990s showed a more accelerated growth trend with clear peaks in 1986 and 1996 as well a significant drop in alliance activity in 1990. This particular, seemingly cyclical, growth pattern is identical to the pattern found for other industries (see Hagedoorn, 1996a).

One possible explanation for the specific pattern in the newly established R&D alliances, found in the MERIT-CATI database is related to the volatility of financial markets during the second half of the 1980s. In the first years of the 1980s venture capital firms invested large amounts of financial resources in capital intensive R&D projects carried out by new biotechnology firms (Hakansson, Kjellberg and Lundgren, 1993; Senker, 1996; Walsh, Niosi and Mustar, 1995). Originally based on university research that led to major scientific and technological changes, nearly all of the new biotechnology companies were founded to commercially exploit promising new technologies such as genetic engineering and cell fusion. For most, if not all, of these small firms, venture capital constituted the single largest source of funding.

After the 1987 Wall Street crash, however, venture capitalists became increasingly hesitant to provide the funds for new biotechnology firms since most of them failed to introduce new breakthrough pharmaceutical products (Barley, Freeman, and Hybels, 1992; Galambos and Sturchio, 1998; Smith and Fleck, 1988; Walsh and Galimberti, 1993). The decreasing availability of venture capital during the second half of the 1980s caused an initial shakeout in the industry with numerous biotechnology firms filing for bankruptcy. The lower number of potential biotechnology R&D partners available to large pharmaceutical companies may provide a tentative explanation for the substantial decrease in the number of newly established partnerships during the final years of the 1980s. Also during these years, the major source of funding for new biotechnology firms shifted from venture capital to large pharmaceutical companies, which shows up in the gradual growth of newly made R&D partnerships during the first half of the 1990s (see also Barley et al., 1992; Senker and Sharp, 1997; Smith and Fleck, 1988).

RATIONALES FOR R&D PARTNERING

In the literature the explanation for the overall increase of alliance activity is generally related to the motives that 'force' companies to collaborate on R&D. Major factors mentioned in that context are related to important industrial and technological changes in the 1980s and 1990s that have led to increased interdisciplinarity of scientific and technological developments, higher risks surrounding R&D, increasing costs of R&D projects, and ever-shortening innovation cycles that favour collaboration (see Contractor and Lorange, 1988; Dussauge and Garette, 1999; Hagedoorn 1993, 1996a; Mowery, 1988; Mytelka, 1991; Nooteboom, 1999; OECD, 1992). In the following we restrict our attention to those rationales that are

important for firms that are engaged in biotechnological activities, in particular large established pharmaceutical companies and new biotechnology firms.

For large pharmaceutical companies their motives to enter into R&D partnerships frequently have both a cost economizing background as well as a strategic intent (see also Eisenhardt and Schoonhoven, 1996; Hagedoorn, 1993; Hagedoorn, Link and Vonortas, 2000; Lorenzoni and Lipparini, 1999; Mowery, Oxley and Silverman, 1998). The cost-economizing motivation appears particularly to play a role when we consider the period that covers the first years of the 1980s. Around this time the pharmaceutical industry at large was confronted with a dramatic increase in R&D costs at the same time as there was a declining number of new drug compounds resulting from the more traditional chemical routes to innovation (Grabowski and Vernon, 1994; Pisano and Wheelwright, 1995; Walker and Walker, 1986).

As a result of these developments, large companies such as Bayer, Ciba Geigy, and Eli Lilly were beginning to reposition themselves in an attempt to achieve greater economies of scale and scope in R&D. One of their main goals was to carry out exploratory basic research across a broader range of new scientific and technological areas in order to identify and take advantage of the many commercial opportunities that were opening up in these fields (Galambos and Sturchio, 1998; Hagedoorn, 1995; Hamel, 1991; Walsh and Galimberti, 1993). However, even the largest, well-financed pharmaceutical companies were finding it more and more difficult to finance both basic and applied research across the entire range of relevant new opportunities. This problem induced many of these firms to seek access to external technological research and knowledge by establishing partnerships with others (Barley et al., 1992; Hagedoorn, 1993; Pisano and Wheelwright, 1995; Powell, 1996, 1998).

During the early 1980s pharmaceutical companies began to develop and maintain numerous formal partnerships with external sources of the new technology, i.e. small biotechnology firms, most of them US-based, and research universities in order to gain a window on the scientific advances in molecular biology and genetic engineering (Arora and Gambardella, 1990; Barley et al., 1992; Hagedoorn and Roijakkers, 2002; Powell, 1996). In these cases the strategic intent of R&D partnerships became more apparent. Adopting this strategy allowed these firms to keep their main R&D activities within their own domain while jointly performing R&D with biotech companies in this new, high-risk area of R&D of which the future importance for their technological capabilities was too unclear to justify any sudden changes in the existing research strategy.

If established companies are motivated to enter partnerships mainly to

lower the cost of some of their R&D activities as well as to explore new technological opportunities beyond their current domain (Arora and Gambardella, 1990; Doz, 1988; Pisano, 1991; Shan, Walker and Kogut, 1994), small firms in turn primarily have a cost-economizing rationale (Senker and Sharp, 1997). Although biotech firms developed a reputation for their R&D capabilities and applied laboratory research in advanced biotechnology, most of them failed to develop pharmaceutical products for sale to final customers. According to Walsh and Galimberti (1993) this was mainly due to a shortage of funds, an extended development cycle, a lower level of demand than anticipated, and their inability to combine obviously novel forms of technical knowledge with knowledge of approval procedures, production and marketing.

The instability of capital markets in the final years of the 1980s was an important motivating factor for small biotechnology firms to form various kinds of partnerships. As already mentioned, during the first half of the 1980s, the initial capital requirements of US-based start-ups were primarily met by venture capital firms (Hakansson et al., 1993; Senker, 1996; Walsh et al., 1995). Between 1980 and 1983, the most successful biotechnology firms that were founded on the basis of academic breakthroughs, such as Genentech, were the first to go public and launch initial stock offerings (IPOs) (Barley et al., 1992). Some of these had disappointing results, but the stock market boom of 1983 triggered a series of initial public offerings and a period of heavy speculation in the stocks of new biotechnology firms. The strong market for IPOs also stimulated many venture capital firms to provide the funding for large numbers of new start-ups, often on just the promise of a new technology. Besides genetic engineering, the ability to produce, at low cost, large quantities of monoclonal antibodies triggered the founding of many entrepreneurial companies as well as a wave of enthusiasm among investors.

Because development work took longer than anticipated, however, and many new biotechnology-based pharmaceuticals proved to be less promising when subjected to rigorous clinical testing, even the oldest biotechnology firms were slow in introducing new breakthrough products (Galambos and Sturchio, 1998; Smith and Fleck, 1988). Venture capital firms typically receive their financing through partnerships, which are normally based on strict contractual arrangements with respect to payback dates. The low chances of recapturing their investments within a relatively short period of time made these firms less willing to finance costly R&D and clinical trials (Barley et al., 1992). As was previously mentioned, after the stock market collapse of 1987, investors became extremely cautious about the potential for new biotechnology-based pharmaceuticals and their interest in IPOs began to diminish. Unable as yet to produce their own working capital,

small firms were consequently experiencing increasing pressure to finance their R&D by entering partnerships with large pharmaceutical firms (Senker and Sharp, 1997; Smith and Fleck, 1988).

Another problem confronting small firms was a lack of the complementary skills, assets and technologies (Teece, 1986) necessary for successful commercial exploitation of the state-of-the-art technological knowledge they clearly possessed. Genetic engineering may provide new routes to existing as well as to new pharmaceuticals, but the required technological know-how must be combined with knowledge of the worldwide market introduction and distribution of safe and effective pharmaceutical products, among others. Such complementary forms of knowledge are possessed by large pharmaceutical companies, which in the past were the dominant innovators in the pharmaceutical industry. In commercial biotechnology it has become common practice for small firms to share their scientific and technical expertise and/or patents in biotechnology with large pharmaceutical firms in exchange for access to the larger firms' financial resources and established organizational capabilities in clinical research, regulatory affairs, manufacturing and marketing (Della Valle and Gambardella, 1993; Hakansson et al., 1993; Larson, 1992; Rothaermel, 2000).

MODES OF COOPERATION

So far we have discussed R&D partnerships in general terms. However, it has to be stressed that in the biotechnology industry R&D partnering takes place through a specific number of organizational modes. In the following we distinguish between a group of equity-based partnerships, such as joint ventures and minority holdings, and a group of so-called contractual agreements, such as joint R&D agreements and R&D contracts. As these modes of cooperation will feature so prominently in the following analysis, we will briefly discuss them further.

Joint ventures are probably the oldest and most well known form of inter-firm partnering (Berg, Duncan and Friedman, 1982; Hladik, 1985). Traditionally, this mode of cooperation accounted for the majority of partnerships in many sectors of industry. In a joint venture, two or more separate parent companies agree to combine their resources and skills in a distinct organizational unit or 'company' that is characterized by shared equity ownership. In the context of R&D partnering, joint ventures have shared R&D as a specific company objective as well as production, marketing, sales, etc. From this brief description of joint ventures it is obvious that equity participation is used in an attempt to lower transaction costs

between the parent companies. Because equity participation creates a relatively high degree of organizational interdependence among the participating companies, the chances of cheating on other partners can be reduced to a large extent. If one partner does not behave in a responsible way, then the whole venture suffers and equity diminishes for all parent companies (Buckley and Casson, 1988).

Minority holdings are another type of equity-based partnership where one company obtains a rather small interest (substantially less than 50 per cent) in another. In the biotechnology industry minority holdings are often coupled with technology exchange agreements. In particular, large pharmaceutical companies are well known for investing in small biotechnology companies in order to explore a promising new field of technology without investing the full amount of resources that would be needed for internal development. If the technology of the small firm becomes more important to the pharmaceutical firm, a takeover can be considered.

During the past decades a number of contractual forms of R&D partnering, in particular joint R&D agreements, have become an alternative to equity-based partnerships. We understand joint R&D agreements to cover technology and R&D sharing by two or more companies through the joint undertaking of research and development projects with shared resources. Research contracts are examples of non-equity partnerships that regulate R&D partnering in which one company, usually a large one, contracts another, frequently small, company, to perform particular research projects. Non-equity agreements are used extensively by large pharmaceutical companies in the biotechnology industry in order to raise their ability to switch their research from one technology to another (Barley et al., 1992; Obleros and MacDonald, 1988).

Recent studies have established that non-equity, contractual forms of R&D partnerships, such as joint R&D agreements and research contracts, have become very important modes of inter-firm collaboration as their numbers and share in the total of partnerships has far exceeded that of equity-based partnerships (Hagedoorn, 1996a; Hagedoorn and Narula, 1996). Whereas equity agreements are often established in order to raise mutual dependence, an increasing number of companies prefer a more flexible relationship with other companies. Especially in high-tech industries such as biotechnology that are characterized by the increasing complexity of technologies, rapid technological changes, and the increasing costs of R&D, even the largest firms are no longer able to monitor all the technological developments that are important for their core markets. Cooperation through more flexible types of agreements enables these firms to monitor several technological developments and, at the same time, allows them to concentrate on a few, most promising, projects internally

(Harrigan, 1985, 1988). If certain technologies turn out to be less successful, contractual arrangements can be terminated relatively easily with only a small financial loss.

Figure 4.2 shows the gradual increase in the relative importance of contractual arrangements compared with equity-sharing partnerships, which is in congruence with previous contributions. All numbers are calculated as three year moving averages and expressed as percentages of the total number of annually, newly established R&D alliances.

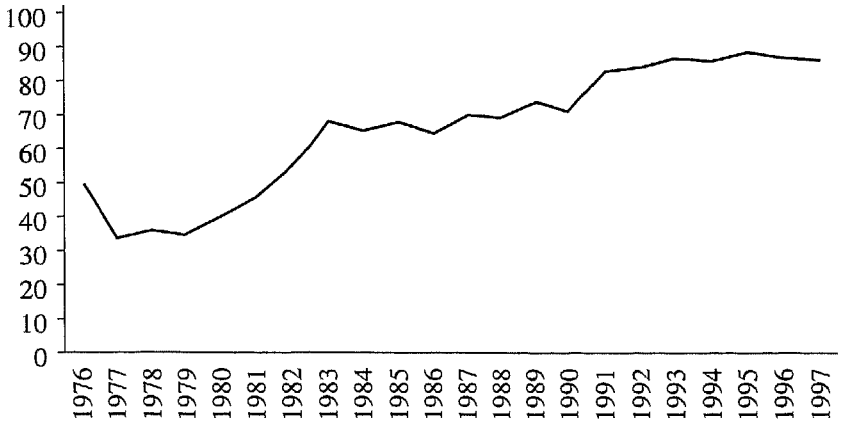

Figure 4.2 Share (%) of contractual modes in all newly established R&D partnerships, three-year moving averages, 1975–98

During the late 1970s, when there were only a small number of R&D partnerships, approximately 60 per cent of new partnerships in the biotechnology industry were equity-based agreements, the majority of these equity-sharing partnerships being of the minority holding type. Fewer than 20 per cent of all the R&D alliances as found in the MERIT-CATI databank were R&D joint ventures. Since the 1980s, the share of contractual arrangements increased from about 60 per cent during most of the 1980s to approximately 85 per cent in the 1990s. In general companies seem to prefer joint R&D agreements to R&D contracts. However, the number of yearly established R&D contracts, found in the CATI database, indicates an increasing popularity of this mode of partnering in recent years.

So far we have presented a general overview of major trends in R&D partnerships in the biotechnology industry since 1975, examining both growth data and the distribution according to major organizational characteristics of these partnerships. These overall trends in inter-firm R&D partnering indicate the following:

- by and large, companies seem to increasingly prefer contractual partnerships to equity-based arrangements,
- the growth of annually newly made R&D partnerships in the biotechnology industry since the early 1980s is primarily caused by an increase in the number of contractual agreements such as joint R&D agreements.

INTERNATIONAL PATTERNS IN R&D PARTNERSHIPS

A considerable number of scholars in business as well as in economics have paid attention to the 'globalization' of the world economy (see e.g. Bartlett, Doz and Hedlund, 1990; Cantwell, 1991; Dunning, 1988, 1993; Hirschey and Caves, 1981; Pearce, 1989; Reich, 1990, 1991; Vernon, 1966, 1979). Globalization is an important and critical feature of today's high technology industries such as biotechnology, where increased international competition between companies forces them to pursue international strategies. Through these international strategies companies do not only seek foreign market entry but also foreign assets (both of a tangible and an intangible nature) and build international inter-firm partnerships for sourcing of R&D, production and supply. Many authors (Contractor and Lorange, 1988; Dunning, 1993; Duysters and Hagedoorn, 1996; Ohmae, 1990; Yoshino and Rangan, 1995) have stressed the critical role that inter-firm R&D partnering plays in the internationalization strategies of a growing number of companies. Consequently, one could expect that the share of international R&D partnerships in the total number of R&D partnerships should have increased during the past two and a half decades.

In this section we will see to what extent inter-firm biotechnology R&D partnerships have become more internationalized, paying special attention to partnerships made between companies from Asia (Japan and South Korea), Europe (the EU and EFTA countries) and North America (USA and Canada). Previous work by Freeman and Hagedoorn (1994) and Ohmae (1985, 1990) revealed that the majority of R&D partnerships are made between companies from within the Triad regions (Japan, Europe and North America). South Korea is mentioned by Freeman and Hagedoorn (1994) and Duysters and Hagedoorn (2000) as a recent 'player' of some importance. In the following, R&D partnerships between companies from Asia, Europe and North America are considered as international alliances, i.e. inter-Triadic partnerships. Intra-European partnerships are seen as regional or domestic partnerships, as are partnerships made within

either Asia or North America. All other combinations outside the Triad regions are treated as a miscellaneous category.

Figure 4.3 demonstrates that a large share of the population of biotechnology R&D partnerships was of an intra-regional or domestic nature during the second half of the 1970s as well as the 1980s. However, this share declined over the past decades, from an average of about 55 per cent for most of the 1980s to somewhat higher than 45 per cent during the 1990s. For most of the 1990s, the share of international, inter-Triadic, partnerships was higher than the domestic and regional alliances. During the final years of the 1990s, the share of domestic alliances rose again relative to international partnerships. Also, during the most recent years there was a growth of the share of other combinations to a still relatively small share of around 2 per cent.

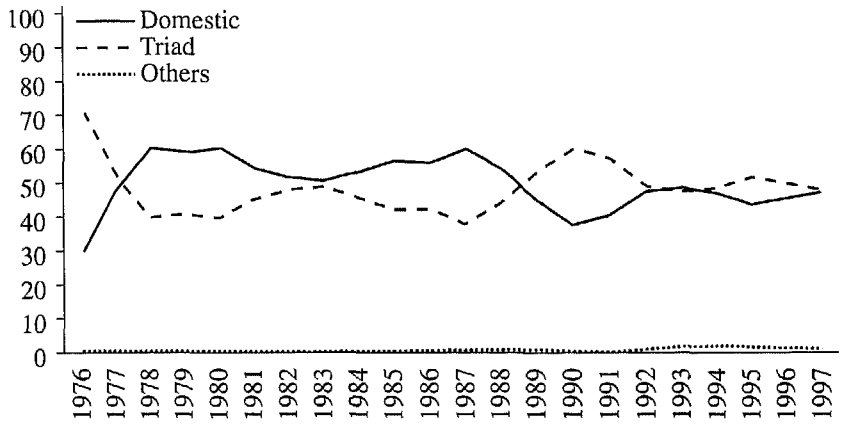

Figure 4.3 Share (%) of international and domestic (regional) partnerships in newly established R&D partnerships, three-year moving averages, 1975–98

So far we have described the general pattern in international biotechnology R&D partnering. Next we examine the role played by the different international economic and trading blocks at a more disaggregated level (see Figures 4.4a–e). If one looks at the overall pattern in R&D partnering during the past two and a half decades, it becomes clear that companies from the Triad participate in over 98 per cent of all R&D partnerships. North America clearly dominates R&D partnering in the biotechnology industry. Over 70 per cent of the R&D partnerships as found in MERIT-CATI for the past two and a half decades have at least one North American partner. During the 1970s and 1980s, the share of partnerships involving at

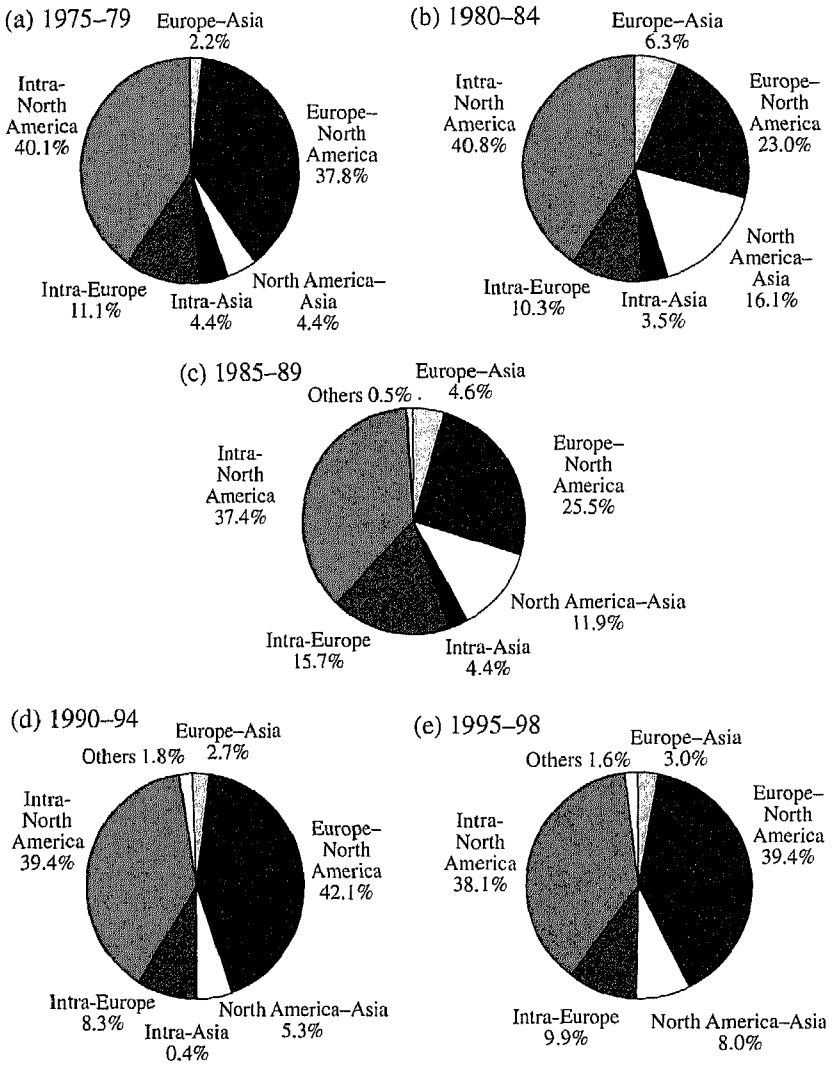

Figure 4.4 International distribution of R&D partnerships; a 1975–79; b 1980–84; c 1985–89; d 1990–94; e 1995–98

least one North American partner gradually eroded from around 82 per cent in the second half of the 1970s to less than 75 per cent in the final years of the 1980s. This share increased again to more than 85 per cent during the 1990s. Partnerships within North America (of which the majority share

involves intra-US R&D partnering; US–Canadian partnerships and intra-Canadian partnerships accounting for less than 4 per cent) account for around 40 per cent of all the R&D partnerships in all periods.

During the second half of the 1970s more than 37 per cent of the inter-firm R&D partnerships were made between European and North American companies. This share fell to a level of less than 26 per cent during the 1980s, after which it increased again to over 39 per cent in the 1990s. These shares are substantially higher than the shares found for intra-European R&D partnerships in identical periods. The share of intra-European partnerships dropped from slightly over 11 per cent in the 1970s to around 10 per cent in the early 1980s. The second half of the 1980s marked a sudden increase in the share of intra-European partnerships to nearly 16 per cent. During the 1990s less than 10 per cent of all R&D partnerships were made between two or more European firms.

North American–Asian R&D partnering grew gradually from about 4 per cent during the 1970s to about 16 per cent during the first half of the 1980s. This share eroded to slightly less than 12 per cent in the late 1980s and to only 5 per cent in the first years of the 1990s. The share of R&D partnerships made between companies from North America and Asia reached 8 per cent during the most recent years. Intra-Asian or intra-Japanese R&D partnerships and partnerships between Europe and Asia remained at a relatively low level of less than 7 per cent during the last two and a half decades.

Further analysis of this data (detailed figures are not shown here) reveals some striking developments in the overall distribution of R&D partnerships at the level of countries. First of all, Swiss firms and companies from the UK and Germany played an important role in Europe–US R&D partnering in all periods considered. The overall dominance of R&D partnering between Europe and the US by UK firms is a development that dates back to the late 1980s. During the 1970s less than 5 per cent of these alliances were made between UK-based companies and US companies, and in the first half of the 1980s they accounted for even less than 3 per cent of all partnerships. However, the second half of the 1980s marked a sudden increase in the share of UK–US partnerships to over 7 per cent. This increase continued well into the 1990s and ultimately reached a level of more than 11 per cent. During the last two and a half decades we also saw R&D partnerships between US companies and companies from France, Sweden, and the Netherlands, although these shares have remained relatively low.

Second, while UK-based firms and companies from Switzerland and Germany have dominated Europe–US R&D partnering in the biotechnology industry during the past decades, these firms have also played

an important role in inter-firm partnering between two or more European companies. In particular, during the 1980s and 1990s, 2–3 per cent of these partnerships were established within the UK. A few other important country dyads are Switzerland–Germany, UK–Sweden, and Germany–France.

Third, Japan–US partnerships represent the largest share of all Asia–North America biotechnology R&D partnering during the 1970s, 1980s and 1990s. During the 1980s and 1990s, South Korea appeared as a relatively important partner to the US besides Japan.

Fourth, if we take a closer look at the pattern in R&D partnering between companies from Asia and Europe, it becomes clear that companies from Japan, Switzerland, and the UK participated in the majority of these alliances during the late 1970s and the 1980s. During the 1990s, Japan–UK partnerships as well as Japan–Germany partnering and to a lesser extent partnerships between Japanese firms and French companies dominated R&D partnering between Asia and Europe. Besides Japan, South Korea appeared as an important partner for French companies.

LEADING COOPERATING FIRMS

In this chapter an attempt is made not only to understand basic trends in the growth of inter-firm R&D cooperation in the international biotechnology industry, but also to reveal the innovative role played by a large group of cooperating companies, i.e. small, entrepreneurial biotechnology firms and large established pharmaceutical companies.

Our understanding of the role played by these different categories of companies can be clearly placed within the Schumpeterian tradition. The importance of the entrepreneurial company as a major generator of new innovations is most clearly stressed in 'early' Schumpeter (1934). In this early work, entrepreneurial companies are small, independent, and act as major agents of change within new industries. These entrepreneurial companies are innovators that successfully introduce new products of which the development is expected to be largely financed through external sources and not so much through internal financial resources (cash-flow).

Many elements of these Schumpeterian entrepreneurial firms are clearly present in the biotechnology industry. In fact both Kenney (1986) and Powell et al. (1996) depict small biotechnology firms as an ideal type of modern entrepreneurial companies. As mentioned by Arora and Gambardella (1990), Pisano (1991), Barley et al. (1992), and Powell et al. (1996), small new biotechnology companies are frequently financed through venture capital or loans and equity participation of large compa-

nies. Originally based on university research that led to major scientific and technological changes, nearly all of the small, biotechnology companies also started as new entrants to the pharmaceutical industry (Kenney, 1986; Pisano, 1990; Powell, 1996).

In terms of their organizational setting and their organizational culture, most of the small biotechnology companies are quite different from the 'standard' company that one finds in traditional industries. New biotechnology companies seem to be driven by scientific discoveries and innovative performance and not only by regular profit-seeking (Lumerman Oliver and Porter Liebeskind, 1997). Also, the 'academic culture' within these innovation-driven and loosely organized companies, with their informal, non-hierarchical structures, sets them apart from many other 'traditional' companies (Pisano, 1991; Powell, 1996).

If we look at the role of large companies in Schumpeter, we have to understand that they play an important part in many of his publications. Specifically the 'older' Schumpeter (1942) pictures a world of 'modern, trustified capitalism' where large science-based companies dominate the innovative environment and where innovation has become routinized in large research laboratories and R&D departments. It is this particular perspective on the role of large companies that for a long period, during the 1950s, 1960s and 1970s, dominated the understanding of the role of large companies as the main source of innovation (see Kamien and Schwartz, 1982; Scherer, 1984).

In the combined biotechnology and pharmaceutical industry, large companies play a dominant role in the more traditional pharmaceutical subsectors (Arora and Gambardella, 1990). Large companies with their extensive R&D activities and their long-term experience with time-consuming clinical trials have come to dominate the innovation process in the traditional pharmaceutical industry. This dominance is based on their leading role in incremental innovation, exploiting their current organic chemical knowledge base and their ability to expand existing portfolios of pharmaceutical products.

Based on the literature discussed, one might expect that the central role of small, entrepreneurial biotechnology firms in R&D partnering, as stressed in the early work of Schumpeter, is likely to be most obvious during the 1980s when many of these new firms introduced major scientific and technological breakthroughs in the pharmaceutical industry. However, as the field of biotechnology has gradually matured, entrepreneurial biotechnology firms have become less important for inter-firm R&D cooperation while large companies may have become more dominant. This more dominant role for large science-based firms in a more routinized innovative environment is particularly stressed in the later writings of Schumpeter. In this

section we will see to what extent small firms and large companies play an important role in the context of the most R&D cooperation-intensive companies in the biotechnology industry. Tables 4.1a–e list the ten companies with most R&D links in each Triad region during the past two and a half decades.[1]

For each region it is obvious that many of the leading pharmaceutical companies, such as Roche and Smithkline Beecham from Europe and Merck and Eli Lilly from the US, are well represented. If we look at the leading companies of biotechnology R&D partnering for Asia, we see that in all periods a number of large and medium-sized Japanese companies such as Kyowa Hakko Kogyo and Chugai Pharmaceutical played an important role in inter-firm R&D partnering. In the years 1975–79 the group of most partner-intensive European companies in the biotechnology industry covered a number of leading pharmaceutical companies. We notice that only two small UK-based biotechnology firms, Celltech and British Biotechnology, played a role of some importance during the 1980s, next to large well-established pharmaceutical companies. However, during the 1990s the position of these companies in the rank order of leading R&D partnering firms decreased while several large firms such as Glaxo from the UK entered the top ranking of cooperating companies.

Small firms such as Chiron, Genex and Biogen already held strong positions in the rank order of most intensely cooperating US-based firms during the second half of the 1970s, followed by large companies such as Schering Plough and Merck. During the 1980s these companies continued to hold strong positions in the group of leading R&D partnering firms, while a number of new young biotechnology firms, such as Amgen, Genzyme, California Biotechnology and T Cell Sciences, entered this group. For this time period the top of the list of the most partner-intensive companies located in the US also covered established pharmaceutical companies such as Bristol Myers, Johnson and Johnson and American Home Products. For the 1990s we notice that a number of new biotechnology firms, such as Oncogene Science, Genelabs Technologies, Gensia Pharmaceuticals and Arqule, entered the group of leading companies of biotechnology R&D partnering, however, the position of small firms relative to large companies decreased to some extent.

In congruence with 'early' Schumpeterian views, the results found for the US are indicative of the significant role played by small, entrepreneurial biotechnology firms in innovation, particularly during the 1980s when the new biotechnology first became relevant to the pharmaceutical industry. The 1990s, however, seem to demonstrate a decreasing importance of these small firms in inter-firm R&D partnering if compared with the role of large pharmaceutical companies. These large companies developed into more

Table 4.1a The top ten companies with R&D partnerships, economic regions, 1975–79

Asia			Europe			North America		
Company (size)	Country		Company (size)	Country		Company (size)	Country	
Dai Ichi Kangyo Bank (Large)	Japan	1	Roche (Large)	Switz.	10	Chiron (Small)	US	10
Mitsubishi (Large)	Japan	1	Ciba Geigy (Large)	Switz.	5	Genex (Small)	US	5
Chugai (Medium)	Japan	1	Procordia Nova (Large)	Sweden	3	Biogen (Small)	US	3
Takeda Chemical (Large)	Japan	1	Sandoz (Large)	Switz.	2	Dow (Large)	US	3
Takara Shuzo (Medium)	Japan	1	Schering (Large)	Germany	2	Schering Plough (Large)	US	3
Taiho (Medium)	Japan	1	Smithkline Beecham (Large)	UK	1	Merck (Large)	US	2
Ajinomoto (Large)	Japan	1	Bayer (Large)	Germany	1	Eli Lilly (Large)	US	2
			Boehringer Ingelheim (Large)	Germany	1	Chevron (Large)	US	2
			Pharmacia (Large)	Sweden	1	Innoven (Small)	US	2
			Grand Metropolitan (Large)	UK	1	Amoco (Large)	US	2

Table 4.1b The top ten companies with R&D partnerships, economic regions, 1980–84

Asia			Europe			North America		
Company (Size)	Country		Company (Size)	Country		Company (Size)	Country	
Mitsui (Large)	Japan	7	Roche (Large)	Switz.	18	Biogen (Small)	US	13
Green Cross (Large)	Japan	6	Celltech (Small)	UK	8	Bristol Myers (Large)	US	12
Dai Ichi Kangyo Bank (Large)	Japan	6	Shell (Large)	Neth.	5	J&J (Large)	US	12
Mitsubishi (Large)	Japan	4	Rhone Poulenc (Large)	France	5	Chiron (Small)	US	11
Shionogi (Large)	Japan	3	Ciba Geigy (Large)	Switz.	5	Amgen (Small)	US	9
Kyowa Hakko Kogyo (Large)	Japan	3	Elf Aquitaine (Large)	France	4	Genex (Small)	US	9
Meiji Seika Kaisha (Large)	Japan	2	Procordia Nova (Large)	Sweden	4	Syntex (Large)	US	7
Yamanouchi (Medium)	Japan	2	Smithkline Beecham (Large)	UK	4	AHP (Large)	US	6
Asahi Chemical (Large)	Japan	2	Bayer (Large)	Germany	4	Eli Lilly (Large)	US	6
Dainippon (Medium)	Japan	2	Novo Nordisk (Large)	Denmark	3	Dow (Large)	US	6

Table 4.1c The top ten companies with R&D partnerships, economic regions, 1985–89

Asia			Europe			North America		
Company (size)	Country		Company (size)	Country		Company (size)	Country	
Sumitomo (Large)	Japan	11	Roche (Large)	Switz.	21	Chiron (Small)	US	22
Kyowa Hakko Kogyo (Large)	Japan	7	Smithkline Beecham (Large)	UK	19	AHP (Large)	US	20
Dai Ichi Kangyo Bank (Large)	Japan	7	Celltech (Small)	UK	11	Eastman Kodak (Large)	US	13
Meiji Seika Kaisha (Large)	Japan	6	Pharmacia (Large)	Sweden	9	American Cyanamid (Large)	US	13
Mitsubishi (Large)	Japan	6	Sandoz (Large)	Switz.	9	J&J (Large)	US	13
Mitsui (Large)	Japan	5	British Biotech (Small)	UK	9	Biogen (Small)	US	12
Yamanouchi (Medium)	Japan	5	Procordia Nova (Large)	Sweden	9	Genzyme (Small)	US	12
Toyo Boseki (Large)	Japan	3	Hoechst (Large)	Germany	8	Dupont (Large)	US	10
Green Cross (Large)	Japan	3	Ciba Geigy (Large)	Switz.	7	California Biotech (Small)	US	10
Takeda Chemical (Large)	Japan	3	Rhone Poulenc (Large)	France	7	T Cell Sciences (Small)	US	9

Table 4.1d The top ten companies with R&D partnerships, economic regions, 1990–94

Asia			Europe			North America		
Company (size)	Country		Company (size)	Country		Company (size)	Country	
Eisai (Medium)	Japan	3	Ciba Geigy (Large)	Switz.	13	Chiron (Medium)	US	12
Ono (Medium)	Japan	2	Glaxo (Large)	UK	12	Merck (Large)	US	11
Mitsubishi Kasei (Large)	Japan	2	Smithkline Beecham (Large)	UK	11	Eli Lilly (Large)	US	10
Japan Tobacco (Large)	Japan	2	Rhone Poulenc (Large)	France	10	AHP (Large)	US	8
Chugai (Medium)	Japan	1	Sandoz (Large)	Switz.	7	Pfizer (Large)	US	7
Kyowa Hakko Kogyo (Large)	Japan	1	Hoechst (Large)	Germany	7	Eastman Kodak (Large)	US	6
Takeda Chemical (Large)	Japan	1	Bayer (Large)	Germany	6	Oncogene Science (Small)	US	5
Sankyo (Large)	Japan	1	Roche (Large)	Switz.	6	Genzyme (Medium)	US	5
Mitsubishi (Large)	Japan	1	Astra (Large)	Sweden	5	Genelabs Technologies (Small)	US	5
Dai Ichi Kangyo Bank (Large)	Japan	1	Celltech (Small)	UK	4	Gensia (Small)	US	5

Table 4.1e The top ten companies with R&D partnerships, economic regions, 1995–98

Asia			Europe			North America		
Company (size)	Country		Company (size)	Country		Company (size)	Country	
Chugai (Medium)	Japan	6	Roche (Large)	Switz.	35	Bristol M-Squibb (Large)	US	20
Kyowa Hakko Kogyo (Large)	Japan	5	Smithkline Beecham (Large)	UK	28	Eli Lilly (Large)	US	20
Ono (Medium)	Japan	4	Glaxo Wellcome (Large)	UK	19	Pfizer (Large)	US	18
Takeda Chemical (Large)	Japan	4	Rhone Poulenc (Large)	France	17	Chiron (Large)	US	16
Sankyo (Large)	Japan	4	Bayer (Large)	Germany	11	Warner Lambert (Large)	US	14
Taiho (Medium)	Japan	3	Hoechst (Large)	Germany	11	J&J (Large)	US	13
Yamanouchi (Medium)	Japan	3	Ciba Geigy (Large)	Switz.	10	Schering Plough (Large)	US	13
Shionogi (Large)	Japan	2	Novo Nordisk (Large)	Denmark	8	Arqule (Small)	US	13
Asahi Chemical (Large)	Japan	2	Basf (Large)	Germany	8	Merck (Large)	US	12
Japan Tobacco (Large)	Japan	2	Astra (Large)	Sweden	8	AHP (Large)	US	10

dominant players with multiple partnerships, a change that is clearly more in line with expectations based on the later writings of Schumpeter. However, the findings for Asia and Europe seem to suggest that it was the large pharmaceutical companies, rather than small firms, that were first to explore the new technological area and that these companies have dominated inter-firm R&D partnering more than large US-based companies (see also Saviotti, 1998).

The explanation for these findings is related to the asymmetric international distribution of small firms specialized in biotechnology (Saviotti et al., 1998; Senker and Sharp, 1997; Walsh et al., 1995). By the late 1970s, over 200 biotechnology start-ups had been set up in the US, but a very limited number in Asia and Europe, with the exception of the UK (Rothwell and Zegveld, 1982). The formation of small, R&D-intensive biotechnology firms is generally considered of crucial importance to the early development and commercialization of biotechnology in the US (Kenney, 1986; Grabowski and Vernon, 1994; Orsenigo, 1989). According to Senker (1996, 1998) a similar explosion of small firms was not occurring in Asia and Europe because these regions were lacking a culture which accommodated a close relationship between basic science, private firms and financed entrepreneurship.

Although many large pharmaceutical companies in Europe and elsewhere had already established significant links to university research during the 1940s, 1950s and 1960s, the early development of biotechnology in the US was to a large extent the result of a unique cross-fertilization between venture capital firms and university scientists whose state-of-the-art research led to major scientific and technological changes. Venture capitalists who recognized the commercial potential of scientific research in biotechnology provided the initial investment funds to small start-ups. Their founders and managers were typically academic entrepreneurs who retained their close ties with universities and research institutes while they were getting their new enterprises underway (Barley et al., 1992; Fransman, 1991).

Senker (1998) mentions a number of other factors to explain why Asia and Europe were only slowly taking advantage of the set of new opportunities provided by advances in biotechnology: shortage of venture capital, lack of knowledge of genetic engineering and its commercial potential by existing European and particularly Japanese firms and, compared with the US, a lower science intensity, as well as less frequent cooperation between public research institutions and industry.

From about 1980, European and Asian governments began to adopt policies aimed at remedying these deficiencies and closing the widening biotech gap with the US. They promoted the creation of small venture capital firms

and exerted strong pressure on both universities and large companies to collaborate in building up the science base in genetic engineering (Galambos and Sturchio, 1998; Senker, 1998). Lagging behind the US by about five years, small biotechnology firms began to emerge slowly in other parts of the world during the 1980s (e.g. Celltech and British Biotechnology in the UK). However, even today the distribution of small biotechnology firms is very asymmetric: there are still many more in the US than in other parts of the world (Saviotti et al., 1998; Senker and Sharp, 1997; Walsh et al., 1995).

CONCLUSIONS

The increasing costs of R&D projects, the need to search for alternative routes to pharmaceutical innovation, the speed of developments in major scientific areas such molecular biology and genetic engineering, and the high risks surrounding biotechnology R&D describe many of the strategic and cost-related factors that have motivated large pharmaceutical companies to enter into various sorts of R&D partnerships. Major aspects of partnering behaviour of small biotechnology firms can be found in attempts to obtain access to skills, assets and technologies that would complement their state-of-the-art R&D capabilities and make up for a shortage of venture capital. As all these phenomena have become critical in the current process of inter-firm competition in the combined pharmaceutical and biotechnology industry, it is no surprise that the absolute number of R&D partnerships has increased dramatically during the past decades.

This growth is, to a very large degree, caused by the number of contractual agreements, i.e. joint R&D agreements and R&D contracts. Equity-sharing agreements (i.e. minority holdings), once the most prominent form of inter-firm R&D partnering, have largely been replaced by contractual arrangements as about 85 per cent of the recently established partnerships are of a contractual nature. This development suggests that partnering in the biotechnology industry demands organizational flexibility with the actual form of the partnership fitted to the strategic needs of the companies that are involved. In this industry where factors such as the increasing interdisciplinarity of technological fields, rapid scientific advances, and the high costs of R&D projects significantly affect inter-firm competition, companies strive to increase their organizational flexibility by engaging in numerous short-term R&D projects with multiple partners.

As demonstrated, the increase in alliances in the biotechnology industry has also led to a larger number of international or inter-Triadic partnerships. In relative terms the growth of these international partnerships has superseded the increase in the number of domestic partnerships or alliances

in the same economic region. An explanation for this specific pattern can be found in the foreign sources of biotechnological know-how that companies seek through international R&D partnerships. In that context the dominance of North America, particularly the US, reflects the important role that this continent plays as a major source of R&D resources and capabilities in pharmaceutical biotechnology. This dominance has not only led companies from other countries, particularly the UK, Switzerland and Germany, to actively search for R&D partnerships with North American companies; the North American dominance of technological development in the biotechnology industry has led to a situation where a large percentage of R&D partnerships are formed between companies within the US.

A major conclusion from the above is that the US has emerged as preeminent in biotechnology R&D primarily on the basis of strong research initiatives on the part of small firms. These research-intensive biotechnology start-ups, an ideal type of modern Schumpeterian entrepreneurs, aided by the large amounts of resources provided by venture capitalists and IPO markets were first to undertake commercialization activities on the basis of the newly acquired knowledge in genetic engineering. In Asia and Europe, however, where the number of small firms is much lower than in the US, it was the large pharmaceutical companies that were first to incorporate the new scientific knowledge into their existing R&D programmes. During the early 1980s, large established firms, particularly from the US and Europe, started to invest heavily in biotechnology research through R&D partnerships with small US start-ups. This largely explains why partnerships within North America and partnerships between European and North American companies account for the majority of all partnerships established during the past two and a half decades.

NOTE

1. Information on size (number of employees) was collected from various sources such as the Institute for Biotechnology Information, the US Securities and Exchange Commission, World Scope Global Researcher, Amadeus, Dun & Bradstreet's Linkages, and Orsenigo (1989). Firms with less than or equal to 500 employees were regarded as small and those having between 501 and 5000 employees as medium sized companies. Firms with over 5001 employees were classified as large companies.

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APPENDIX 4.1 THE MERIT-COOPERATIVE AGREEMENTS AND TECHNOLOGY INDICATORS (CATI) DATABANK

The MERIT-CATI databank (see Hagedoorn, 1993) contains information on nearly 10000 cooperative agreements in various sectors, ranging from high technology sectors such as IT and biotechnology to less technology intensive sectors such as chemicals and heavy electrical equipment. Systematic collection of inter-firm partnerships started in 1987. If available, many sources from earlier years were consulted to establish a retrospective overview. In order to collect detailed information about inter-firm partnerships, various sources are consulted: newspaper and journal articles, books dealing with the subject, and in particular specialized journals that report on business events.

This method of information gathering has some drawbacks and limitations due to the lack of publicity for certain arrangements, and the low profile of certain groups of companies and fields of technology. Despite these shortcomings, which are difficult to circumvent even by extensive and large-scale data collection, we have been able to obtain a clear overview of the joint efforts of many companies. This enables us to perform empirical research, which goes beyond single-firm case studies.

The databank contains information on each cooperative agreement and some information on companies participating in these agreements. Cooperative agreements are defined as mutual interests between independent industrial partners that are not linked through majority ownership. In the CATI databank, only those agreements that involve either a technology transfer or some form of jointly undertaken R&D are being recorded. Information is also collected on joint ventures in which new technology is received from at least one of the partners, or on joint ventures having some R&D programme. Other types of agreements such as production and marketing alliances are not included. In other words, this material is primarily related to R&D collaboration and technology cooperation, i.e. those agreements for which a combined innovative activity or an exchange of technology is at least part of the agreement. We regard as relevant information for each partnership: the number of companies involved; names of companies; year of establishment; and modes of cooperation. Important information on participating companies includes their location, and names of parent companies.